ASSOCIATION OF BENZENE EXPOSURE WITHINSULIN RESISTANCE AND OXIDATIVE STRESS IN A SAMPLE OF CHILDREN AND ADOLESCENTS

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Abstract: -
Background: Benzene is a ubiquitous environmental pollutant with several adverse health effects. The aim of this study was to investigate the association of urinary benzene metabolite (t,t-ma) withoxidative stress and insulin resistance (IR) in children and adolescents.
Methods: This cross-sectional study was conducted among 86 children and adolescents,aged 6-18 years, in Isfahan, Iran. T,t-ma was measured as urinary benzene metabolite and homeostasis model assessment (HOMA-IR) was determined as an index of IR. Malondialdehyde (MDA) and superoxide dismutase (SOD) were measured as markers of oxidative stress.
Results: We found significant association between t,t-ma concentrations and insulin resistance, fasting blood glucose, and fasting blood insulin ($P<0.05$). Moreover, after adjustment for age, sex, and the state of having smoking parents, statistically significant increase in SOD and MDA (4.49 and 3.54 fold respectively) was observedin intermediate levels of t,t-ma vs.its low levels ($P<0.05$).
Conclusion: This is the first study to investigate the association of benzene metabolites withIR and oxidative stress in the pediatric age group. It showed that exposure of children to benzene , even in environmental levels, can be a predisposing factor for chronic diseases in later years of life.

Key Words - Benzene, Urinary metabolites, Insulin resistance, Oxidative stress, Children

I. INTRODUCTION

Benzene is a ubiquitous volatile organic pollutant, which is released to environment from a variety of sources such asindustry effluents, oil-refining plants[1]urban traffic, car refueling and smoking. Moreover, foods may be contaminated with benzene ,and some kinds of cooking and food processing procedures can increase trace amounts of this chemical in food, such as barbecuing, grilling, smoking, canning and irradiation[2, 3].

Formerly the focus of studies was on occupational concentrations of benzene but nowadays, concernshave shifted to the long-term effects of exposure to low levels of benzene[4]. Trans,trans-muconic acid(t,t-ma) is one of the most sensitive and reliable benzene urinary biomarkers, with aconversion rate of 2-25%, depended on the benzene exposure level [5]. Insulin resistance (IR),which is known to be the major cause of type 2 diabetes is the state of theimproper ability of tissues to respond insulin[6].It is suggested that oxidative stress which is defined as an imbalance between pro-oxidant and antioxidant factors, may induce insulin resistance[7].
A recent study showed significant association betweenurinary benzene metabolite and IR in elderly population[8]Children may have greater exposure to benzene, because of their smaller size, increased activity, and increased ventilation rates, as compared with those of adults, in the air on a unit-body-weight basis[9].This study aims to determine the associationbetween urinary benzene metabolite (t,t-ma)and oxidative stress and IR in children and adolescents.

II. METHODS

This cross-sectional studywas conducted amongchildren and adolescents aged 6-18 years, living in Isfahan, the second large city in Iranwith high air pollution.A total of 86children participated inthis study. Inclusion criteria werenot having consumed soft drinks and industrial food productions 24 hours before urine and blood sampling in order to avoid the confounding effect of sorbic acid [10].
Data on $PM_{2.5}$ was obtained from the Isfahan Department of Environment. Written informed consent was signed by participant's parents prior to participation, and oral assent was obtained from participants. Fasting venous blood samples were obtained for fasting insulin, fasting blood glucose, malondialdehyde (MDA) and superoxide dismutase (SOD).IR was determined by homeostasis model assessment of insulin resistance(HOMA-IR)[11]. Urinary benzene was determined using a urinary ring opened benzene metabolite, trans, trans muconic acid were measured by gas chromatography-mass spectroscopy (GC/MS)[12].

HOMA-IR levels were modeled in tertiles. Tertile groups were categorized as "low IR","intermediate IR" and "high IR". MDA and SOD were also classified as tertiles.The analysis was performed by

means of STATA (version 11.0, STATA Corp, College Station, TX, USA). Analysis of variance, Kruskal-Wallis test,and Chi-square testswere used for comparison of variables.Ordinal logistic regression was used to analyze theassociation between urinary benzene metabolites and IR.

RESULTS

The mean age of the studypopulation was 10.7(2.7) years. The participants' characteristics are presented in Table 1.

Table1. Characteristics of the study populati

Characteristic	Mean (SD)
Age (yr)	10.75(2.7)
Gender [boy; n (%)]	27(29%)
BMI (kg/m2)	21.97(5.25)
Fasting insulin	9.81(6.93)
Fasting glucose(mg/dL)	90.22(7.81)
HOMA-IR	2.21(1.65)
Urinary tt-ma (ng/L)	0.0195(0.02)
MDA (ng/L)	21.79(9.21)
SOD	152.28(70.68)
$PM_{2.5}$(mcg/m^3)	30.14(2.77)
SBP (mm Hg)	90.52(18.98)
DBP (mm Hg)	56.79(12.78)

BMI = Body mass index; SBP= Systolic blood pressure;DBP= Diastolic blood pressure; FBG= Fasting blood glucose; HOMA index: Fasting insulin × Fasting glucose / 405.

Ordinal logistic regression indicated that benzene metabolite increased the risk of IR by 13.3 fold.Statistically significant increase in SOD and MDA (4.49 and 3.54 fold respectively) was observed, in intermediate levels of t,t-ma vs low levels of t,t-ma(Table2).

Table 2. Association of urinary t,t-MA levels with insulin resistance and oxidative stress in ordinal logistic regression model

	Tertiles	Crude OR (95%CI)	P-Value	Adjusted OR* (95%CI)	P-value
HOMA-IR					
t,t-ma	1st tertile	1		1	
	2nd tertile	2.44(0.95-6.25)	0.06	2.66(0.87-8.15)	0.08
	3rd tertile	7.66(2.75-21.33)	<0.001	13.3(3.94-44.9)	<0.001
MDA					
t,t-ma	1st tertile	1		1	
	2nd tertile	1.97(0.77-5.07)	0.16	3.54(1.10-11.34)	0.034
	3rd tertile	1.26(0.47-3.33)	0.65	1.81(0.60-5.46)	0.29
SOD					
t,t-ma	1st tertile	1		1	
	2nd tertile	2.79(1.05-7.4)	0.04	4.49(1.42-14.2)	0.01
	3rd tertile	1.57(0.58-4.25)	0.37	1.93(0.64-5.73)	0.24

*Models were adjusted for age, Sex, BMI passive smoking.

t-t-MA: Trans,trans-muconic acid; IR: Insulin resistance; MDA:Malondialdehyde; SOD: Superoxide dismutase

DISCUSSION

To the best of our knowledge, this is the first study to investigate the association betweenbenzene metabolites and IR in the pediatric age group.In this study, significant positive association was found between benzene exposure and IR in children.Afteradjustment for potential confounders, an increase in oxidative stress markers was observedin intermediate levels of benzene exposure.
Two German birth cohorts showed that long-termexposure to traffic-related air pollution increased the risk of IR in children with 10 years of age [13].Another cohort study suggestedpositive association between traffic-related air pollution and incidence of type 2 diabetes among elderly women[14].

A recent study reported the associationbetween benzene exposure andIR in elderly adults.It was also mentioned that urinary t,t-ma level was positively associated with urinary levels of MDA as the biomarker of oxidative stress[8]. Results of our study showed that higher concentrations of benzene metabolite increased the risk of IR by 13.3 fold.In an animal study, exposure to $PM_{2.5}$ increased the risk ofIR[15].

Some limitations of this study are, having small sample size, the cross-sectional nature and the fact that we have only one measurement of t,t-ma concentrations; but for a more accurate data double measurement is needed.

CONCLUSION

Our findings on the association of benzene exposure with increased risk of IR propose that non-occupational daily exposures to benzene can be a risk factor for chronic diseases later in life.

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